

(19) 日本国特許庁 (JP)

(12) 公表特許公報 (A)

(11) 特許出願公表番号

特表2005-533038

(P2005-533038A)

(43) 公表日 平成17年11月4日 (2005.11.4)

(51) Int. Cl. ⁷

F I

テーマコード (参考)

C O 7 D 409/12

C O 7 D 409/12

C S P

4 C O 6 3

A 6 1 K 31/4184

A 6 1 K 31/4184

4 C O 8 6

A 6 1 K 31/454

A 6 1 K 31/454

A 6 1 P 1/04

A 6 1 P 1/04

A 6 1 P 3/06

A 6 1 P 3/06

審査請求 未請求 予備審査請求 有 (全 61 頁) 最終頁に続く

(21) 出願番号 特願2004-509675 (P2004-509675)

(86) (22) 出願日 平成15年5月26日 (2003.5.26)

(85) 翻訳文提出日 平成17年1月18日 (2005.1.18)

(86) 国際出願番号 PCT/EP2003/005465

(87) 国際公開番号 W02003/101984

(87) 国際公開日 平成15年12月11日 (2003.12.11)

(31) 優先権主張番号 102 24 892.3

(32) 優先日 平成14年6月4日 (2002.6.4)

(33) 優先権主張国 ドイツ (DE)

(71) 出願人 397056695

アベンティス・ファーマ・ドイチュラント
・ゲゼルシャフト・ミット・ベシュレンク
テル・ハフツングドイツ連邦共和国デー 6 5 9 2 9 フラン
クフルト・アム・マイン、ブリュニングシ
ユトラーセ 5 0

(74) 代理人 100091731

弁理士 高木 千嘉

(74) 代理人 100127926

弁理士 結田 純次

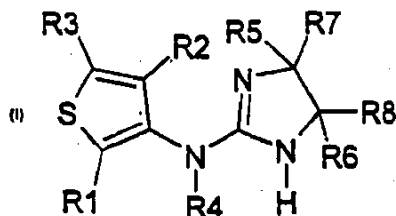
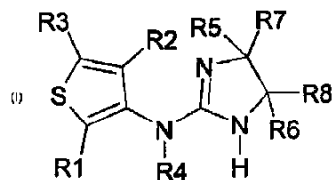
(74) 代理人 100105290

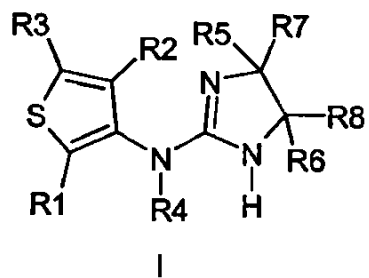
弁理士 三輪 昭次

最終頁に続く

(54) 【発明の名称】 置換チオフェン、その製造方法、医薬または診断薬としてのその使用、および、これを含有する
医薬

(57)





10

$$q \quad 2q$$

2

n

3

k

20

$$n \quad 2m+1$$

k

3

2

3

$$r \quad 2r$$

30

$$2 \quad 5$$

3

6

$$3 \quad 5$$

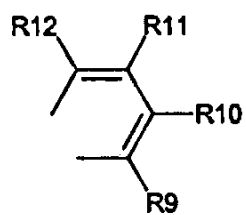
2

5

4

6

40



50

3 2 2 3

2

2

n q $2q$

10

3 k

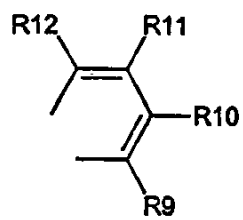
20

n $2m+1$

3 3 2 3

2 2

30



40

50

2

n q 2 q

3

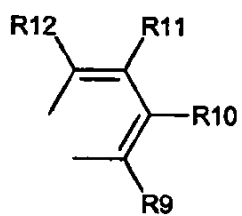
k

3

10

3

3



20

30

n q 2 q

3

k

3

40

, , , , ,

, , , , ,

50

10

,

20

,

,

,

,

,

,

,

,

,

30

40

50

10

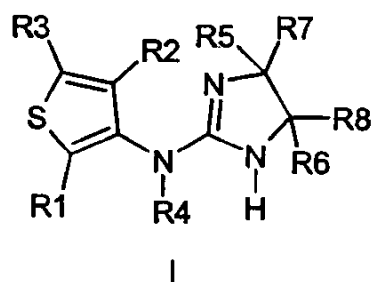
20

30

40

respiratory drive

50



10

$$q \quad 2q$$

$$2 \quad n$$

$$3 \quad k$$

20

$$n \quad 2n+1$$

3

$$k \quad 3 \quad 2$$

30

$$r \quad 2r$$

$$2 \quad 5$$

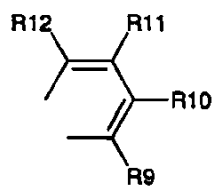
$$3 \quad 6$$

$$3 \quad 5$$

$$2 \quad 5$$

$$4 \quad 6$$

40



10

3

2

2

3

2

2

 $n \quad q \quad 2q$

20

3

k

30

 $n \quad 2m+1$

2

n

 $q \quad 2q$

40

3

k

 $n \quad 2m+1$

k

3

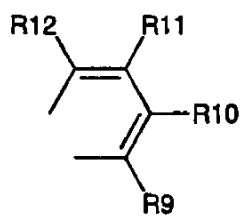
2

3

50

$q \quad 2q$
 $2 \quad 5$
 $3 \quad 5$
 $3 \quad 6$
 $2 \quad 5$
 $4 \quad 6$

10



20

 $3 \quad 2 \quad 2 \quad 3$

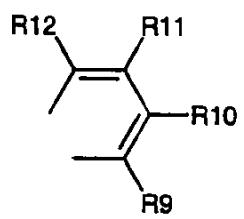
30

 $2 \quad 2$
 $n \quad q \quad 2q$
 $3 \quad k$

40

 $n \quad 2m+1$
 $3 \quad 3 \quad 2 \quad 3$
 $2 \quad 2$

50



10

20

 $n \quad q \quad 2q$

3

k

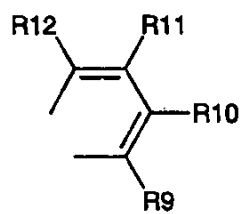
30

3

3

3

40



10

$$n \quad q \quad 2q$$

3

k

20

3

, , , , ,
 , , , , ,

30

40

50

,

,

,

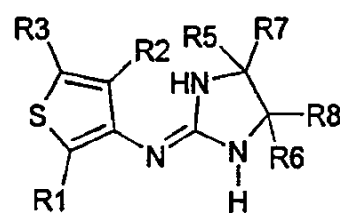
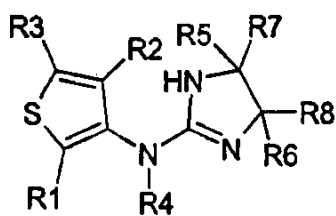
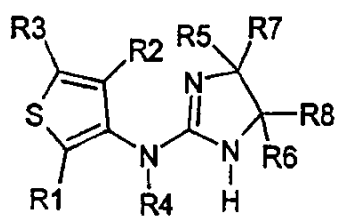
,

,

10

20

30



(もし R4=Hであるなら)

40

,

,

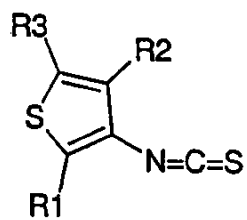
50

10

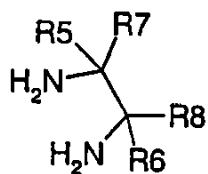
II

III

20



II



III

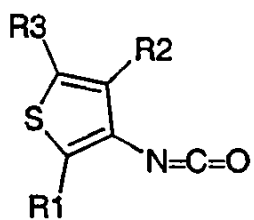
30

II

40

II

IV



IV

50

III

10

.

50

20

.

.

30

40

.

.

50

10

20

30

40

50

10

20

30

40

50

(selecting proteins)

VII

10

20

30

omapatrilat

gemopatrilat

40

50

10

20

30

40

50

10

2 +

20

30

40

50

10

20

30

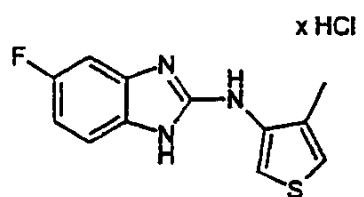
40

2

2

50

2 •

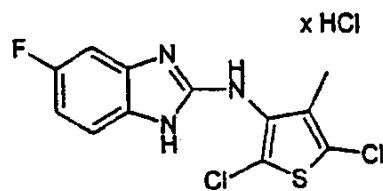
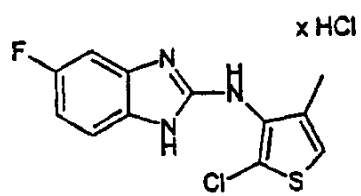


40

10

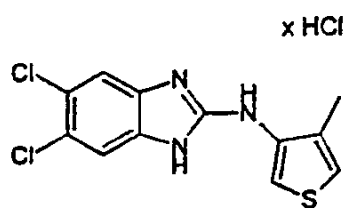
20

30



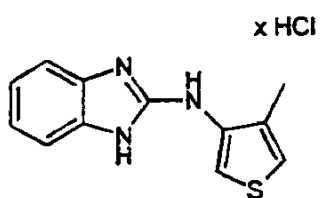
40

50



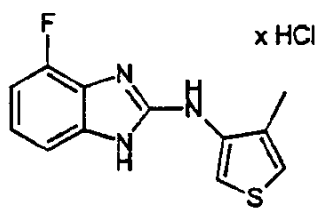
10

20



30

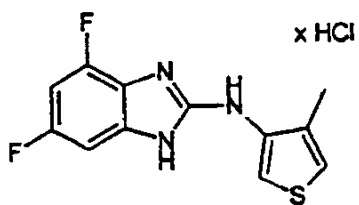
40



10

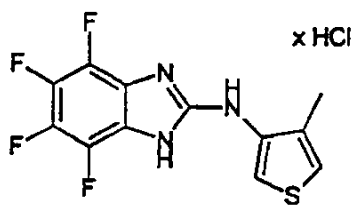
20

30



40

50



, , ,

, , ,

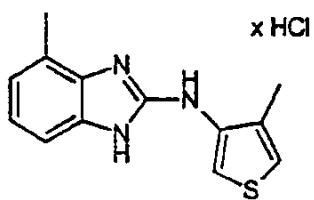
10

,

, , ,

, , ,

20

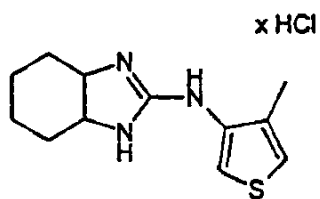


30

,

40

, , , , , ,



50

,

, , , , ,

.

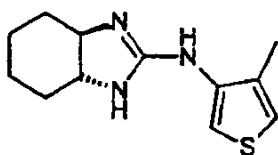
10

.

, , , , ,

 $\times \text{HCl}$

20



,

,

,

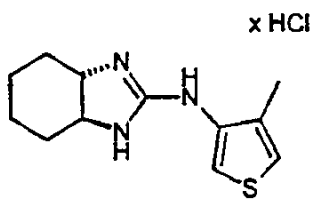
30

, , , , ,

,

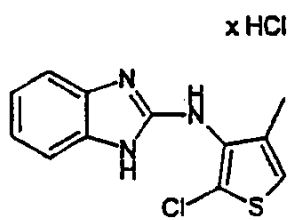
40

, , , , ,

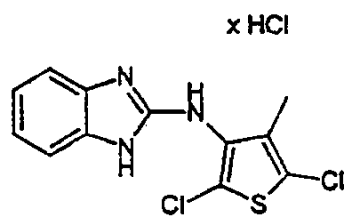


10

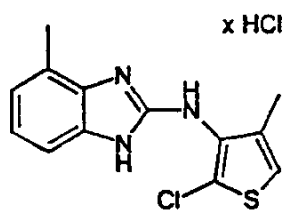
20



30

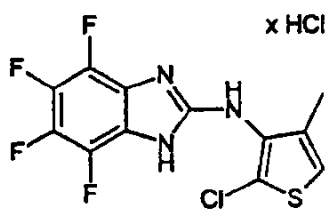


40



10

, , ,

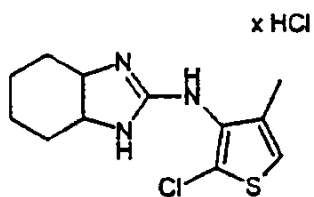


20

, , ,

, , , , ,

30



, , , , ,

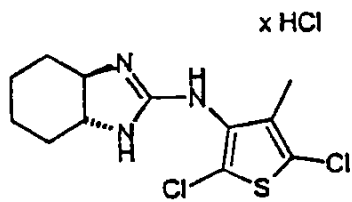
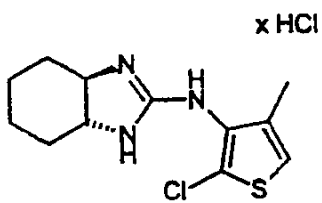
40

,

, , , , ,

, , ,

, , , , ,



, , , , , ,

10

, ,

, , , , ,

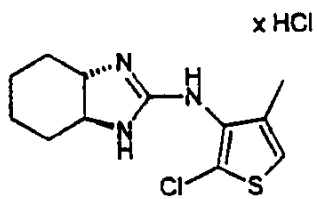
,

, , , , ,

20

,

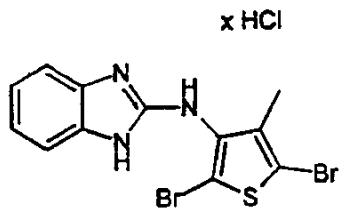
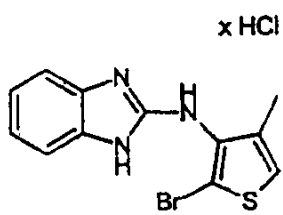
, , , , ,



, , , , , ,

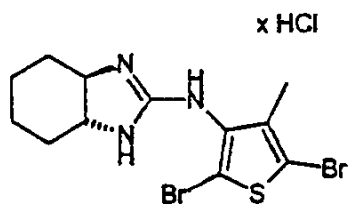
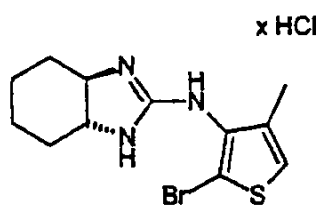
30

,

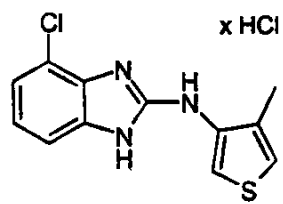


40

50



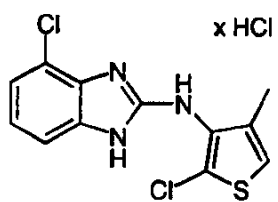
10



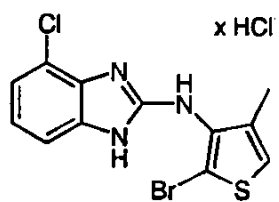
30

40

50

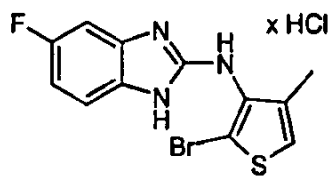


10

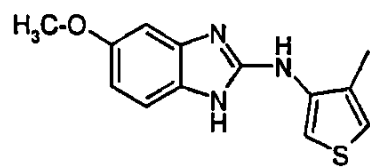
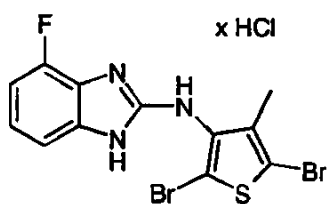


20

30



40



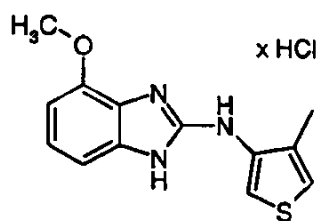
COc1ccc2c(c1)c(c[nH]2)Nc3cc(C)cc(s3)Cl x HClCOc1ccc2c(c1)c(c[nH]2)Nc3cc(Cl)c(s3)C x HCl

1 2

COc1ccc2c(c1)c(c[nH]2)Nc3c(Cl)c(Cl)c(s3)N

1

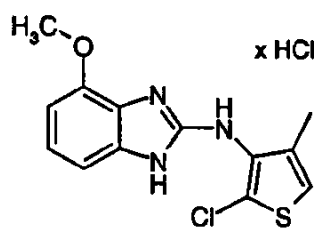
50



10

20

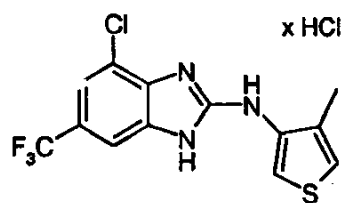
30



40

1
2

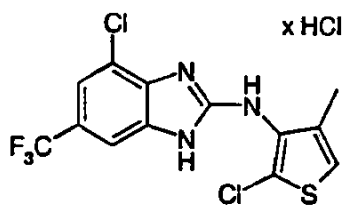
50



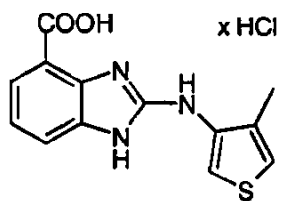
10

20

30



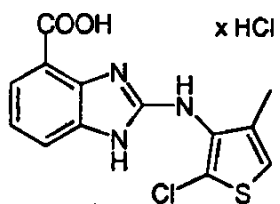
40



10

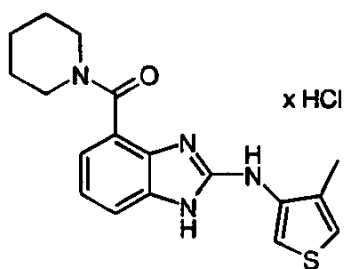
,

20

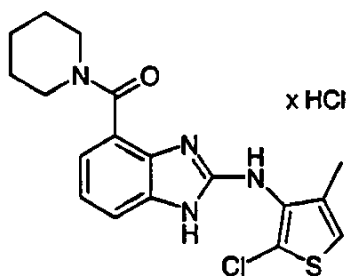


30

40



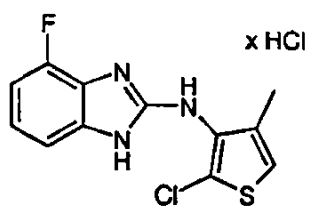
50



10

1 2

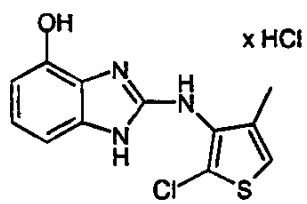
20



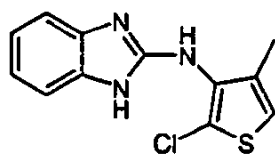
30

1 2

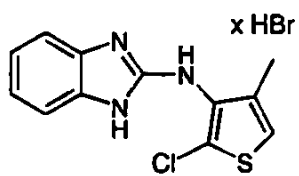
40



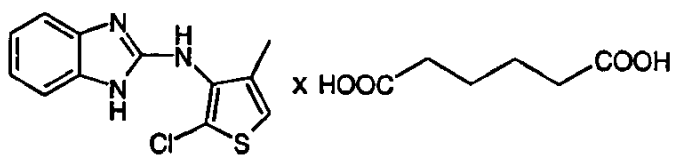
10



20

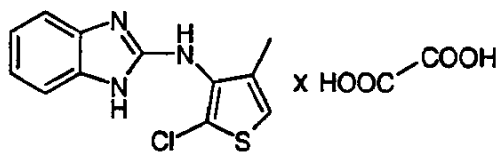


30

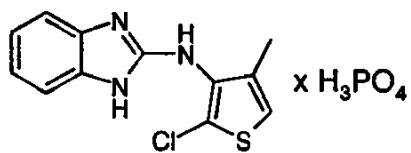


40

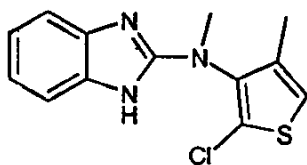
50



10



20



30

40

+

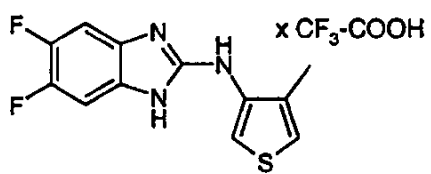
+

.

.

,

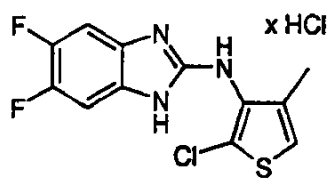
50



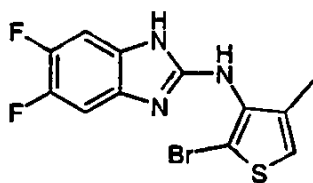
10

20

30



40



10

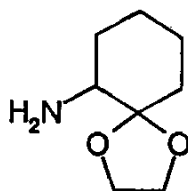
4

+

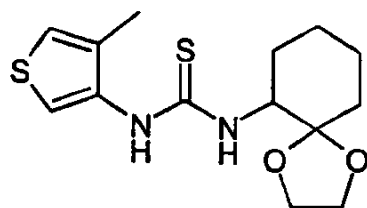
+

20

, , ,



30



40

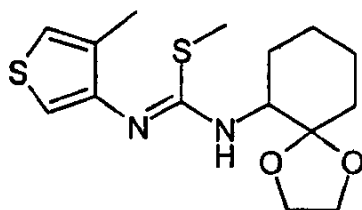
50

4

+ + .

, .

10



, .

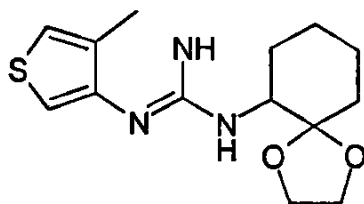
20

4

+ + .

, .

30

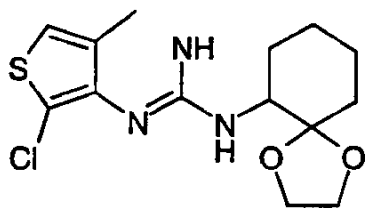


, 40

+ + .

,

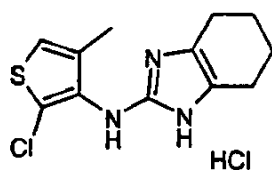
.



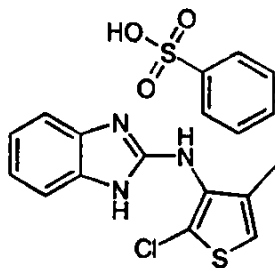
10

4

20

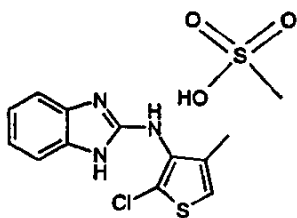


30



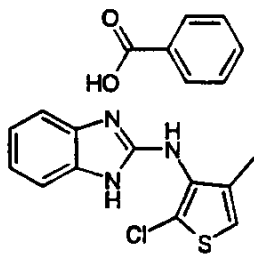
40

50



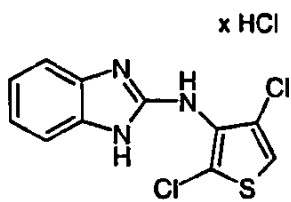
10

20



30

,



x HCl

40

,

2 2 .

.

,

10

20

.

.

2

30

.

.

40

,

.

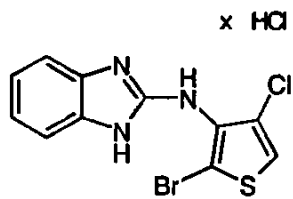
.

.

50

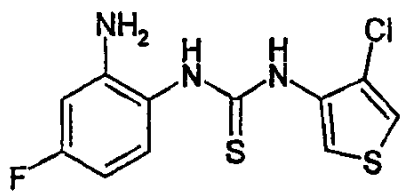
10

20



30

40



,

10

4

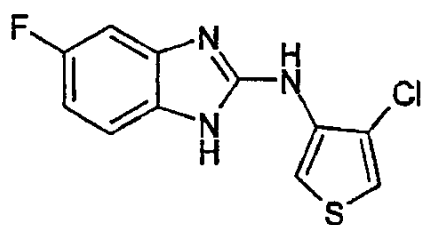
+

+

.

.

20



30

+

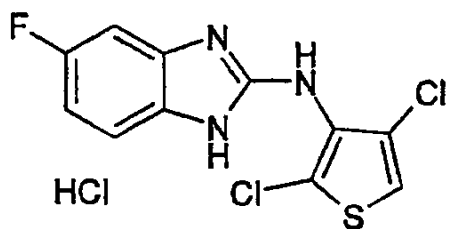
+

.

.

,

40

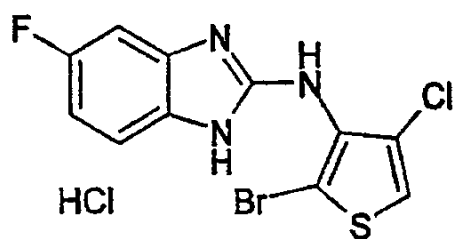


50

4

10

+ + .



20

4

30

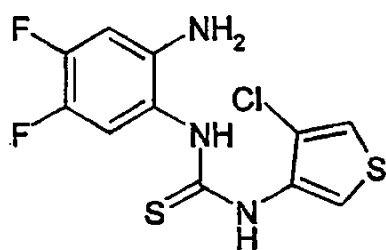
+ + .

,

,

,

40

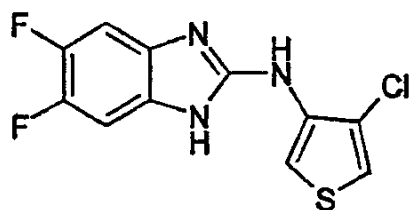


,

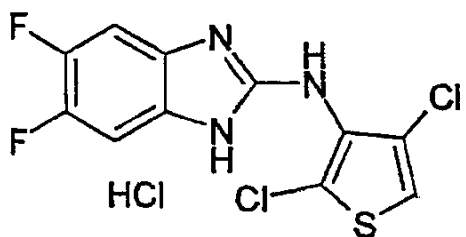
,

.

50



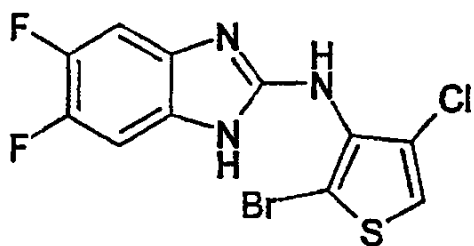
10



30



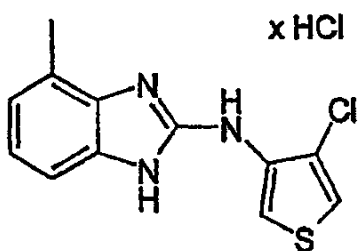
40



,

10

+ + .

 $x \text{ HCl}$

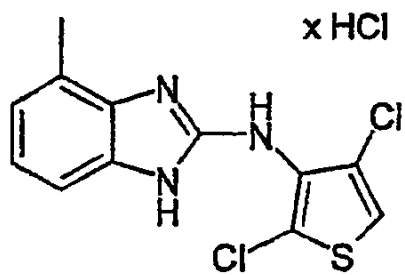
20

30

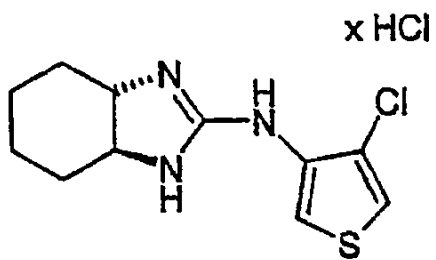
,

40

,



10



20

, ,

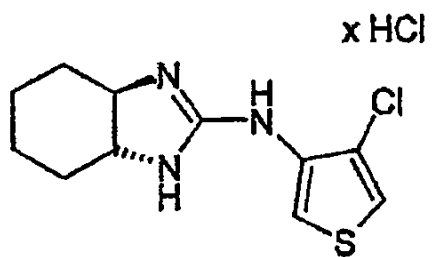
30

, , ,

40

,

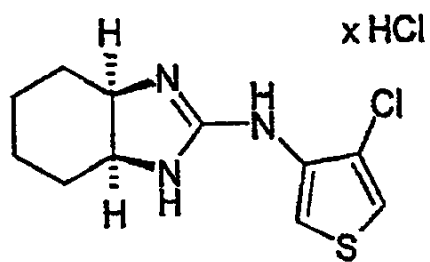
, , , , ,



10

20

30



40

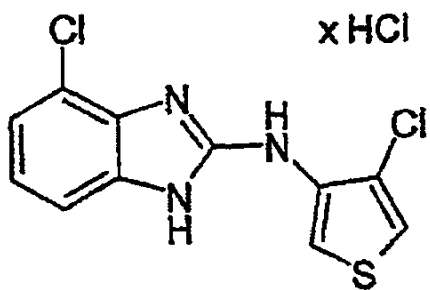
50

10



30

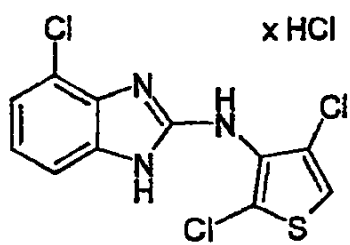




10

20

30



40

50

,

’ ’ ’ ’ ’

,

’ ’ ’ ’ ’

,

,

,

10

,

20

$$\cdot \quad \cdot \quad)$$

30

4

•

4

2

•

4

4

+

•

•

•

2

•

2

•

2

4

•

2

4

40

+

•

•

•

2

•

2

2

4

•

2

4

+

実施例	IC ₅₀ [μ M]
16 トランス-R,R-2-クロロ-3N- (3a, 4, 5, 6, 7, 7a-ヘキサヒドロ-1H-2-ベンズイミダゾリル) -4-メチル-3-チエニルアミン塩酸塩	0.27 (rNHE3)
12 2-クロロ-3N- (2-ベンズイミダゾリル) -4-メチル-3-チエニルアミン塩酸塩	0.12 (rNHE3)
54 2-ブロモ-4-クロロ-3N- (2-ベンズイミダゾリルアミノ) チオフェン塩酸塩	0.22 (hNHE3)
53 2,4-ジクロロ-3N- (2-ベンズイミダゾリルアミノ) チオフェン塩酸塩	0.14 (hNHE3)
56 2,4-ジクロロ-3N- (4-メチル-2-ベンズイミダゾリルアミノ) チオフェン塩酸塩	0.22 (hNHE3)
60 トランス-R,R-2,4-ジクロロ-3N- (3a, 4, 5, 6, 7, 7a-ヘキサヒドロ-1H-2-ベンズイミダゾリル) -3-チエニルアミン塩酸塩	0.19 (hNHE3)
63 2,4-ジクロロ-3N- (4-クロロ-2-ベンズイミダゾリルアミノ) チオフェン塩酸塩	0.54 (hNHE3)
38 2-クロロ-3N- (4-ヒドロキシ-2-ベンズイミダゾリルアミノ) -4-メチルチオフェン塩酸塩	0.84 (hNHE3)
18 2-ブロモ-3N- (2-ベンズイミダゾリル) -4-メチル-3-チエニルアミン塩酸塩	0.12 (hNHE3)
19 トランス-R,R-2-ブロモ-3N- (3a, 4, 5, 6, 7, 7a-ヘキサヒドロ-1H-2-ベンズイミダゾリル) -4-メチル-3-チエニルアミン塩酸塩	0.56 (hNHE3)
2 2-クロロ-3N- (5-フルオロ-2-ベンズイミダゾリル) -4-メチル-3-チエニルアミン塩酸塩	0.62 (hNHE3)
44 (1H-ベンズイミダゾール-2-イル) - (2-クロロ-4-メチルチオフェン-3-イル) -メチルアミン	1.59 (hNHE3)

10

20

30

40

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 03/05465

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D409/12 A61K31/4168 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 758 476 A (LINDNER E ET AL) 11 September 1973 (1973-09-11) cited in the application column 1, line 30 - line 46; examples 1, 4B, 7	1-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Z document member of the same patent family

Date of the actual completion of the international search

9 September 2003

Date of mailing of the international search report

19/09/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5816 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Härtinger, S

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/05465

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
US 3758476	A	11-09-1973	DE 1941575 A1	04-03-1971
			DE 1941761 A1	25-02-1971
			AT 310157 B	25-09-1973
			AT 310158 B	25-09-1973
			AT 304535 B	10-01-1973
			BE 754820 A4	15-02-1971
			BE 754935 A1	17-02-1971
			CA 1011738 A1	07-06-1977
			CH 544116 A	28-12-1973
			CH 554894 A	15-10-1974
			CH 555358 A	31-10-1974
			CH 530415 A	15-11-1972
			FR 2068493 A6	27-08-1971
			FR 2068505 A5	27-08-1971
			GB 1324646 A	25-07-1973
			GB 1312133 A	04-04-1973
			NL 7011708 A ,B,	18-02-1971
			NL 7011933 A	16-02-1971
			SE 368406 B	01-07-1974
			US 3814758 A	04-06-1974
			DK 144035 B	23-11-1981
			ES 410034 A1	01-12-1975
			ES 410035 A1	01-12-1975
			FI 57412 B	30-04-1980
			IE 34428 B1	14-05-1975
			IL 35093 A	14-01-1974
			JP 54016500 B	22-06-1979
			NO 129573 B	29-04-1974
			PL 81180 B1	30-08-1975
			SU 399126 A3	27-09-1973
			SU 423297 A3	05-04-1974
			SU 404244 A3	26-10-1973
			YU 206970 A ,B	31-10-1978
			ZA 7005543 A	28-04-1971

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 03/05465

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES

IPK 7 C07D409/12 A61K31/4168 A61P11/00

Nach der internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)

IPK 7 C07D A61K A61P

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

EPO-Internal, WPI Data, PAJ, BIOSIS, BEILSTEIN Data, CHEM ABS Data

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	US 3 758 476 A (LINDNER E ET AL) 11. September 1973 (1973-09-11) in der Anmeldung erwähnt Spalte 1, Zeile 30 - Zeile 46; Beispiele 1, 4B, 7 -----	1-13

☐ Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen☒ Siehe Anhang Patentfamilie

* Besondere Kategorien von angegebenen Veröffentlichungen :

A Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist

E älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist

L Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)

O Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht

P Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist

T Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist

X Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden

Y Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist

Z Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der internationalen Recherche

9. September 2003

Absenddatum des internationalen Recherchenberichts

19/09/2003

Name und Postanschrift der Internationalen Recherchenbehörde

Europäisches Patentamt, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Bevollmächtigter Bediensteter

Härtinger, S

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen

PCT/EP 03/05465

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
US 3758476 A	11-09-1973	DE 1941575 A1	04-03-1971
		DE 1941761 A1	25-02-1971
		AT 310157 B	25-09-1973
		AT 310158 B	25-09-1973
		AT 304535 B	10-01-1973
		BE 754820 A4	15-02-1971
		BE 754935 A1	17-02-1971
		CA 1011738 A1	07-06-1977
		CH 544116 A	28-12-1973
		CH 554894 A	15-10-1974
		CH 555358 A	31-10-1974
		CH 530415 A	15-11-1972
		FR 2068493 A6	27-08-1971
		FR 2068505 A5	27-08-1971
		GB 1324646 A	25-07-1973
		GB 1312133 A	04-04-1973
		NL 7011708 A ,B,	18-02-1971
		NL 7011933 A	16-02-1971
		SE 368406 B	01-07-1974
		US 3814758 A	04-06-1974
		DK 144035 B	23-11-1981
		ES 410034 A1	01-12-1975
		ES 410035 A1	01-12-1975
		FI 57412 B	30-04-1980
		IE 34428 B1	14-05-1975
		IL 35093 A	14-01-1974
		JP 54016500 B	22-06-1979
		NO 129573 B	29-04-1974
		PL 81180 B1	30-08-1975
		SU 399126 A3	27-09-1973
		SU 423297 A3	05-04-1974
		SU 404244 A3	26-10-1973
		YU 206970 A ,B	31-10-1978
		ZA 7005543 A	28-04-1971

(51) Int.Cl.⁷

3/10	3/10
9/04	9/04
9/06	9/06
9/10	9/10
9/12	9/10
11/00	9/12
13/08	11/00
13/12	13/08
25/00	13/12
25/08	25/00
25/22	25/08
25/24	25/22
29/00	25/24
33/00	29/00
33/06	33/00
35/00	33/06
39/02	35/00
43/00	39/02
	43/00

(81) AP(GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZM,ZW),EA(AM,AZ,BY,KG,KZ,MD,RU,TJ,TM),EP(AT, BE,BG,CH,CY,CZ,DE,DK,EE,ES,FI,FR,GB,GR,HU,IE,IT,LU,MC,NL,PT,RO,SE,SI,SK,TR),OA(BF,BJ,CF,CG,CI,CM,GA, GN,GQ,GW,ML,MR,NE,SN,TD,TG),AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ, EC,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,M W,MX,MZ,NI,NO,NZ,OM,PH,PL,PT,RO,RU,SC,SD,SE,SG,SK,SL,TJ,TM,TN,TR,TT,TZ,UA,UG,UZ,VC,VN,YU,ZA,ZM,ZW

(72)

(72)

(72)

(72)

(72)

(72)

() 4C063 AA01 BB09 CC92 DD26 EE01
 4C086 AA01 AA02 AA03 BC39 GA04 GA07 MA01 MA04 NA14 ZA01
 ZA05 ZA06 ZA12 ZA36 ZA37 ZA42 ZA45 ZA54 ZA59 ZA68
 ZA75 ZA81 ZB11 ZB26 ZB35 ZB37 ZB38 ZC33 ZC37